MONOCLONAL ANTIBODIES AGAINST GLYCOPROTEIN OF EBOLA SUDAN BONIFACE VIRUS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/239,166, filed Sep. 2, 2009 and U.S. Provisional Application No. 61/290,725, filed Dec. 29, 2009, which are hereby incorporated by reference in their entirety.

RIGHTS IN THE INVENTION

[0002] This invention was made with support from the United States Government and, specifically, the United States Army Medical Research Institute of Infectious Diseases and, accordingly, the United States government has certain rights in this invention.

FIELD AND BACKGROUND OF THE INVENTION

[0003] The invention is related generally to the field of antibodies, and specifically to monoclonal antibodies against the Ebola Sudan Boniface virus (SBEBOV).

[0004] Ebola hemorrhagic fever is a disease in humans, chimpanzees, and monkeys, caused by infection with Ebola virus, and associated with high mortality. This virus was first recognized in Zaire, Africa in 1976. The exact origin and location of Ebola virus is still unknown. Ebola virus is one of only two known members of a family of RNA viruses, the Filoviridae. (The other member is the Marburg virus). Ebola virus (EBOV) is an enveloped, non-segmented, negative-strand virus. The virus causes a severe hemorrhagic fever disease with a high mortality rate and there are no licensed vaccines or therapeutics approved for human use. To date, most published reports have focused on exposure to a subtype of EBOV isolated from the Zaire region in 1976, Ebola virus Zaire (ZEBOV). ZEBOV is believed to have the highest mortality rate in humans (90%) of the different subtypes of Ebola.

[0005] In 1976, the Sudan subtype of the Ebola virus (SEBOV) was discovered concurrently with the Zaire subtype when simultaneous, but separate, outbreaks of Ebola hemorrhagic fever erupted in the nations of Sudan and Zaire, respectively. This new isolate was named Sudan Boniface Ebola virus (SBEBOV). The Sudan subtype has been responsible for four outbreaks of Ebola hemorrhagic fever, including the largest ever Ebola virus outbreak in Uganda in 2000 and 2001, with 425 cases and 224 deaths. This outbreak marked the reemergence of the Sudan subtype after 21 years, and originated close to the city of Gulu near the Uganda-Sudan border. The virus isolated from this outbreak was named Sudan Gulu Ebola Virus (SGEBOV). In 2004, a smaller epidemic occurred near the city of Yambio in southern Sudan, very near the location of the 1976 outbreak. Infection with SBEBOV and SGEBOV was 40-65% lethal in the human population. Genomic sequence of both the SBEBOV and the SGEBOV was determined and is 95.3% identical at the amino acid level. However, the sequence of SBEBOV and SGEBOV is only 54.2% and 54.6% identical to ZEBOV, respectively.

[0006] The Ebola genome shows a linear gene arrangement with the following protein coding regions—nucleoprotein (NP)—viral structural protein—(VP) 35—VP40 glycoprotein (GP)—VP30—VP24—and, polymerase (L). To date, four species of Ebola virus have been identified: Ebola Zaire, Ebola Sudan, Ebola Ivory Coast, and Ebola Reston. Different strains have been identified among within the species. Ebola Zaire consists of four identified strains, Zaire Maying a, Zaire-95, Eckron-76, and Gabon-94. Ebola Sudan consists of Sudan Boniface and Sudan Maleo-79. Ebola Reston consists of Reston and Reston Siena/Philippine-92. Ebola Ivory Coast consists of only one known strain, Ivory Coast-94. All four known species of Ebola virus have infected humans, but with differing degrees of lethality between species and even among different strains of the same species. Zaire Maying a and Zaire-95 are the two most lethal forms of the Ebola virus, killing approximately 85% of all known infected humans. Zaire Gabon, Sudan Boniface, and Sudan Maleo-79 are less lethal, killing between 53 and 66% of its victims.

[0007] The majority of research in the filovirus community has focused on the Zaire virus species of EBOV; however, the Sudan ebolavirus (SEBOV) species is of similar public health concern. There are known murine monoclonal antibodies that recognize Ebola Zaire glycoprotein (Science, 3 Mar. 2000, volume 287, pp. 1664-1666, Wilson et al., Epitopes Involved in Antibody-Mediated Protection from Ebola Virus). The Zaire monoclonals are disclosed in U.S. Pat. Nos. 6,630,144 and 6,875,433 and U.S. patent application Ser. Nos. 60/560,086, 10/384,976 and 10/696,633, all of which are incorporated by reference in their entirety herein. However, no antibodies against the Sudan Boniface species of the Ebola Virus are known to exist.

[0008] Ebolavirus (EBOV) causes a severe hemorrhagic fever with up to 90% human mortality (1). Outbreaks of EBOV have become increasingly more frequent (four in the last two years, including appearance of EBOV infection in domesticated swine), yet no vaccines or treatments are approved for human use (2). Five species have been identified: Sudan, Zaire, Côte d'Ivoire, Reston and the proposed Bundibugyo (1, 3), although almost all human deaths have been the result of infection with either Sudan ebolavirus (SEBOV) or Zaire ebolavirus (ZEBOV). Indeed, SEBOV and ZEBOV were the first two species of ebolavirus to be identified, with their names derived from simultaneous outbreaks in 1976 in the nations of Sudan and Zaire, respectively. This original SEBOV outbreak was caused by a viral strain termed Boniface. However, a new SEBOV strain emerged in October 2000 in northwestern Uganda. This strain, termed Gulu, triggered the largest outbreak of Ebola hemorrhagic fever yet described, involving at least 425 individuals, of whom 224 died (4).

[0009] Multiple monoclonal antibodies against ZEBOV have been developed (5-10), however, not one has been shown to neutralize SEBOV. SEBOV is 40% divergent in sequence and antigenically distinct from ZEBOV. Consequently, the development of antibodies that neutralize SEBOV is critical for provision of therapeutics and for further development and improvement of broad-range vaccines.

[0010] Ebolavirus entry is a multi-step process including attachment of virions to target cells, internalization of virions into the endosome, and fusion of the virus with the endosomal membrane for release of viral contents into the cytoplasm. The surface glycoprotein GP is the sole EBOV protein responsible for attachment, fusion and entry. Hence, GP is a critical component of vaccines and the target of neutralizing antibodies.

[0011] The role of anti-GP antibodies in protection is confounded by the observation that Ebola GP occurs in several